Bowditch (H. P.)

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BY

H. P. BOWDITCH, M. D.,
Professor of Physiology in Harvard University.

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THE ACTION OF SULPHURIC ETHER ON THE PERIPHERAL NERVOUS SYSTEM.

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PROFESSOR OF PHYSIOLOGY IN HARVARD UNIVERSITY.

IN an article on "The Respiratory Function of the Human Larynx" in the *N. Y. Medical Journal* for July 4, 1885, Dr. F. H. Hooper recorded the observation that stimulation of the recurrent laryngeal nerves of dogs causes a dilatation of the glottis when the animals are thoroughly etherized, but a constriction when they are slightly or not at all under the influence of the drug. As the phenomenon occurred equally well whether the stimulation was applied to the intact nerve or to its peripheral end after section it was evident that the action of the drug must be either upon the peripheral portions of the nerve or upon the muscles.

In order to decide between these alternatives, and to ascertain whether similar observations could be made upon other groups of antagonistic muscles supplied by a single nerve trunk, experiments were undertaken by Mr. J. W. Perkins, interne at the Children's Hospital, Boston, in the autumn of 1885.

The sciatic nerve of the frog, with the groups of flexor and extensor muscles which it supplies, was selected for purposes of experiment. The frog was prepared by destroying the medulla and cord. The sciatic plexus was dissected out on both sides and shielded electrodes placed on the nerves close to their origin from the cord. The frog was then suspended in such a way that the hind legs hung freely in fluid contained in two beaker glasses, one leg being immersed in a 0.5 per cent. solution of common salt and the other in a similar solution to which three per cent. of sulphuric ether had been added.

Tetanic stimulation of the sciatic plexus was produced by a Du Bois Reymond induction apparatus having a secondary coil consisting of 10,260 turns of fine wire and graduated with arbitrary units of intensity

such that the maximum stimulation, produced by pushing the secondary completely over the primary coil, corresponded to 1000 units of intensity.

The experiment consisted in applying, at short intervals, a tetanic stimulation of very weak intensity ($I = 0.5 - 2$) to each sciatic plexus in turn and observing the position of the legs as one of them gradually came under the influence of the ether. It was observed that at the beginning of the experiment stimulation produced the same effect on both sides; viz., extension of the leg and abduction of the toes. After the ether had been applied five or ten minutes this effect gave place to a flexion of the leg and adduction of the toes, and after about twenty minutes the stimulation failed to produce any effect. Stimulation of the nerve on the side where the leg was immersed in the salt solution produced the same extension as in the beginning of the experiment. The solutions were now interchanged so that the etherized leg was suspended in the salt solution, and *vice versâ*. As the effect of the ether disappeared from the leg in the salt solution the stimulation of the nerve produced at first flexion and adduction which afterward gave place to extension and abduction as at first. This experiment was repeated with very constant results upon five different frogs.

It thus appears that there is a stage in ether narcosis when stimulation of the nerve, which ordinarily produces extension and abduction, causes the opposite effects and this action can be observed both when the narcosis is coming on and when it is passing off. For the sake of brevity, this action of ether will be termed the "ether effect." The phenomenon is apparently the same as that observed by Hooper on the larynx and, so far as the physiological action of ether is concerned, the constrictors of the larynx seem to correspond to the extensors, and the dilators of the larynx to the flexors of the leg, an analogy the reverse of that which was maintained by Rosenbach,[1] who was led to his conclusions by pathological considerations.

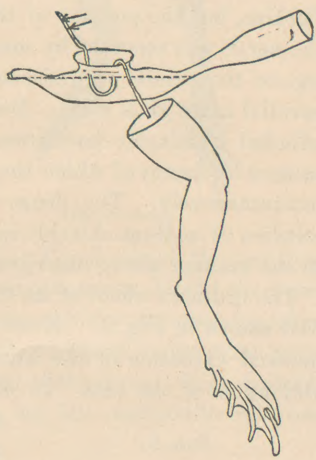
Since in these experiments the central nervous system was destroyed, it is obvious that this "ether effect" must be at the periphery, but whether upon the nerve trunks, the nerve terminations, or the muscular fibres cannot be decided from the above experiments.

To study this question the following experiment was performed. The sciatic nerve was freed from its connections for a distance sufficient to permit the portion of the nerve between the electrodes and the muscles to be immersed in a solution of ether. This was most readily effected by means of a bent glass tube, with a hole blown in the side, such as is represented in Fig. 1. The tube was bent or inclined at such an angle that fluid introduced by means of a pipette into the upper end would flow down and cover a loop of the nerve and could at the same

[1] Bresl. ärztl. Zeitschr., 1880, Nos. 2 and 3.

time be readily washed away and replaced by another fluid introduced in the same way. Five experiments performed in this way gave results which were very constant and quite similar to those obtained when the ether was applied to the skin of the leg. The only important difference was that the action of the ether was much more prompt when applied directly to the nerve, complete paralysis taking place in about seven minutes. The "ether effect" manifested itself both in flexion and adduction and occasionally in peculiar twisting movements of the phalanges due to unequal stimulation of the various muscles. The important observation was also made that whenever flexion was obtained it could be converted into extension *by increasing the intensity* of the stimulation.

FIG. 1.



From these experiments we are justified in concluding that the "ether effect" is a phenomenon dependent upon the action of the drug upon the nerve fibres themselves, though, of course, the possibility of a simultaneous action upon the muscles is not excluded. An attempt was made to ascertain whether any such action of the drug upon the muscles really occurs by poisoning a frog with curare and applying electricity directly to the limb while immersed in a solution of ether.

It was found, however, to be practically impossible to apply the electricity in such a way as to stimulate uniformly all the muscles of the limb and thus produce a movement comparable with that obtained when the muscles are stimulated through the nerve. The experiments made in this way were, therefore, inconclusive. It is evident, however, that the observed action of ether on the nerve trunks is sufficient to explain the "ether effect," and since, when one sufficient cause is demonstrated, it is illogical to assume the existence of another, we may conclude for the present that the phenomenon in question concerns exclusively the nerve fibres.

We must next inquire whether the ether can be supposed to exercise an elective action upon the fibres contained in the nerve trunk and to paralyze the fibres supplying the extensor and abductor muscles before it affects those which go to the flexor and adductor group, or whether some simpler and more probable explanation can be suggested.

The above-mentioned observation that flexion could be converted into extension by increasing the intensity of the stimulation, suggests the idea that the "ether effect" may be simply *partial paralysis* of the nerve

fibres. On this hypothesis we should expect to find that stimulation of the nerve with a *very weak* current would cause flexion of the limb, even without the application of ether.

To test this question and also to study the effect of various other reagents besides ether upon the nerve trunk, a series of experiments on frogs were undertaken in the spring of 1886, by Dr. F. W. Ellis.

In these experiments the frog was prepared in the same way as by Perkins, but the position of the legs resulting from the stimulation of the nerve was recorded by means of photography. For this purpose the legs of the animal were suspended in water contained in a large cell with parallel plate glass sides. Behind the cell a piece of opaque white glass afforded a suitable background and in front was placed a dry plate camera by means of which the position of the legs could be photographed instantaneously. The drugs used were mixed with one-half per cent. solution of sodium chloride in distilled water and applied to the nerve in the manner above described.

The ordinary effect of an electrical stimulation of the sciatic nerve is well shown in Fig. 2.[1] Even with quite weak currents there is ordinarily marked extension of the knee, ankle, and toes, accompanied by strong abduction of the toes. In other words, the position of the leg is that assumed when the animal is just completing a vigorous stroke in swimming.

FIG. 2.

EFFECTS OF ETHER.—In the experiments with ether, solutions of the drug varying in strength from one-half to five per cent., were employed. A three per cent. solution was most frequently used and gave, upon the whole, the best results. The observations of Perkins were in the main confirmed—*i. e.*, there was found to be a stage in the paralyzing action of the drug when stimulation of the nerve caused the leg to assume a position contrary to that occasioned by the same degree of simulation without ether. Instead of extension at the knee and ankle, there might be flexion; instead of extension and abduction of the toes, there might be flexion or adduction, or both. It was rare that all these contrary effects were manifested at once. There was generally a predominance of one, and frequently only one was manifested. These "ether effects" were obtained with some frogs more easily than with others, and were not always constant for the same frog. They were generally better obtained when

[1] This and the following figures are photoelectrotype reproductions of photographs taken in the manner above described. As the frogs were suspended with their ventral surface toward the camera the right leg of the animal appears on the left of the figure, and *vice versâ*.

the nerve was recovering from the effects of ether (*i. e.*, after removal of the ether solution from the tube and washing the nerve with saline solution) than when it was coming under the influence of the drug.

FIG. 3.

Ether on nerve.

FIG. 4.

Ether removed.

Figs. 3–8 illustrate these "ether effects." Fig. 3 shows the position assumed by the left leg on irritation of the sciatic nerve during the local application of ether. Fig. 4, the position assumed by the same leg after the removal of the ether. Here flexion and adduction under ether gave place to extension and abduction on removal of the drug. Figs. 5 and 6 show a similar "ether effect" on the right leg, but confined in this case to the muscles moving the toes.

FIG. 5.

Ether on nerve.

FIG. 6.

Ether removed.

In Figs. 7 and 8 the "ether effect" manifests itself in a flexion of the foot and adduction of the toes combined with a strong extension of the leg.

The local application of ether to the nerve was found not to affect the irritability of the nerve below the point of application. This was shown by experiments in which electrodes were placed upon the nerve, both above and below the ether tube. When powerful stimulation applied above the tube no longer caused contraction of the muscles,

a very slight current applied below would produce the usual effect. The ether, therefore, seemed to produce a change in the nerve at the point of application, which rendered it incapable of transmitting the

FIG. 7.

Ether on nerve.

FIG. 8

Ether removed.

ordinary nerve impulse, complete paralysis resulting when the action of the drug was pushed to its extreme, and the so-called "ether effects" during intermediate stages.

Experiments with chloroform and alcohol showed that the "ether effects" could be obtained with these drugs also, although not so strikingly as with ether. A full discussion of the action of these and other drugs will be given on a future occasion.

It was also found, as had been previously observed by Perkins, that an increase in the intensity of the stimulation caused the "ether effect" to disappear, and the ordinary effect of nerve irritation (viz., extension and abduction) to take its place. This led to experiments on the effect of variation in the intensity of the stimulus, and particularly on the

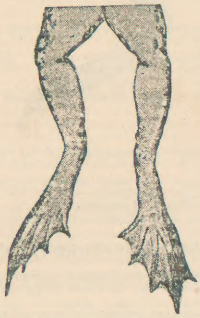
EFFECTS OF VERY WEAK CURRENTS.—The first experiments showing the effect of very weak stimulation were accidental. It was noticed occasionally, when the right sciatic plexus was very strongly stimulated in order to ascertain whether the application of ether to the nerve of that side had produced complete paralysis, that movements of flexion were produced in the leg of the opposite side. These were obviously due to the escape of electricity upon the left plexus, and it was observed that a still further increase in the intensity of the stimulus applied to the right plexus caused the ordinary movements of extension and abduction on the left side. It was subsequently found that by employing weak currents it was generally possible to cause movements (viz., flexion and adduction), which were ordinarily excited by very much stronger stimuli after the application of ether to the nerve. To produce these effects, it was necessary to use currents of very feeble intensity. These were best obtained by separating the secondary coil of the induction apparatus forty or fifty centimetres from the primary, and then turning it round a vertical axis. When flexion and adduction had been obtained in this

way it was always possible to produce the ordinary movements of extension and abduction by increasing the intensity of the stimulation. Occasionally, as a result of very weak stimulation, twitchings or clonic contractions of the muscles were produced. These seemed to be due to a conflict between opposing sets of muscles.

FIG. 9.

Weak irritation.

FIG. 10.



Strong irritation.

Figs. 9–13 illustrate the effects of variations in the intensity of the stimulation applied to unetherized nerves. Fig. 9 shows the position assumed by the left leg under the influence of a very feeble stimulus applied to the sciatic nerve of that side, and Fig. 10 the effect of a stronger stimulus applied to the same nerve.

FIG. 11.

Weak irritation.

FIG. 12.

Strong irritation.

Figs. 11 and 12 show, in a similar manner, the effect of increasing the intensity of the stimulus applied to the right sciatic nerve. Fig. 13 shows the effect of a weak irritation of the left sciatic nerve, and by comparing the position of the left leg in this figure with that of the right leg in Fig. 2, a good idea can be obtained of the great variety of movement which can be produced by changes in the intensity of the stimulation.

These experiments by Ellis prove beyond a doubt that the effects observed by Perkins on stimulating a nerve immersed in a solution of ether, can be obtained with other drugs, and often with very weak currents without any drug. Without ether, flexion and adduction are to be obtained only with very feeble currents, but with ether much stronger stimulation produces the same effect. In both cases, however, an increase in the intensity of the stimulus causes these movements to give place to extension and abduction; the effect of the ether may, therefore, be said to consist in transferring the point, on the scale of intensity, at which the effect of nerve irritation changes from flexion and adduction to extension and abduction from the region of weak to that of relatively strong stimulation.

FIG 13.

Weak irritation.

The "ether effect," as observed in the sciatic nerve of the frog, may be best explained by supposing that a partial paralysis of the nerve by the drug converts what would naturally be a strong into a weak irritation, and that this weak irritation affects only the flexor group of muscles because these are, for some reason or other, more irritable than their antagonists. A stronger irritation or a removal of the ether causes extension, since when both flexors and extensors are stimulated, the position of the leg is determined by the latter—*i. e.*, the more powerful group.

The question of the difference in irritability of the flexors and extensors of the frog's leg and the cause thereof has been much discussed. The fact that a feeble irritation of the sciatic causes flexion, and a strong irritation extension of the leg was first observed by Ritter in 1798, but the subject was first thoroughly investigated by Rollett in 1874–75.[1] This observer experimented with the amputated leg suspended in the air, and also with the muscles attached to myographic levers, and reached the conclusion that the cause of the greater irritability of the flexors was to be sought in the nerve fibres or in their mode of attachment to the muscles. Bour,[2] also, while criticising some of Rollett's methods, found that when the irritation was applied to the upper portion of the sciatic nerve, the flexors were called into action by a feebler stimulus than the extensors.[3]

1 Sitzungsberichte der Wiener Acad. Dritte Abth., lxx. S. 7; lxxi. S. 33; lxxii. S. 349.

2 Verhandl. d. Phys. med. Gesells. in Würzburg. N. F. viii. 221.

3 Dr. W. P. Lombard has kindly made a few experiments upon the irritability of the muscles moving the knee-joint of the frog, using for the purpose the delicate apparatus employed by him in studying the reflex actions of the frog (Archiv für Physiologie, 1885, p. 408). These experiments, though interesting in themselves, are not conclusive as to the relative irritability of the flexor and extensor groups of muscles. The evidence, however, seems to be slightly in favor of the above mentioned conclusion of Bour.

There seems, therefore, to be no doubt that the flexor apparatus of the frog's leg responds to a feebler simulation than the extensor, but whether the cause of this difference lies in the nerve fibres, the muscle fibres, or in the mode of connection between the two, must be left for future investigations to determine. It is not impossible that the microscope may reveal histological differences between the different sorts of muscles similar to those described by Ranvier and others between the red and white muscles of the rabbit.

We must now inquire whether the above explanation of the "ether effect," as studied on the sciatic nerve of the frog, is applicable to the action of the drug, as observed by Hooper, on the recurrent laryngeal nerve of the dog.

A single observation upon a chloralized dog is reported by Hooper, in which a thread passed through the nerve and left in position for several days produced an effect analogous to that of ether on the sciatic nerve of the frog, viz., abduction of the vocal cord on irritation of the nerve on the side thus operated upon, while the same irritation on the opposite side produced the ordinary effect, viz., adduction. As all attempts to repeat this observation failed, no importance can be attached to it. On the other hand, it had never been observed in Hooper's experiments that feeble irritations caused a dilatation of the glottis, while stronger ones caused a constriction, but, as the effect of *very feeble* stimuli had not been specially studied, it was thought desirable, in view of the positive results obtained by Ellis on the frog, to make a few additional experiments directed to this particular point. Experiments were accordingly made upon chloralized dogs, with the result of showing that feeble irritations differed from strong ones in the extent but not in the character of the movements produced. Nothing resembling a dilatation of the glottis could be produced by diminishing the intensity of the stimulus.

When this point had been reached in the study of the question, a paper entitled "The Function of the Recurrent Laryngeal Nerve," by F. Donaldson, Jr., B.A., M.D., appeared in *The American Journal of the Medical Sciences* for July, 1886. In this paper the writer gave an account of experiments on dogs similar to those made by Hooper, but leading to different results, for Donaldson, though unable to obtain the above described "ether effect," did observe a dilatation of the glottis when the recurrent nerve was irritated with *very weak* stimuli. This observation is, therefore, precisely in harmony with Ellis's results obtained upon frogs, and if confirmed would lead to the conclusion that the "ether effect" is in these cases also an effect of partial paralysis.

Shortly after the appearance of Donaldson's article a paper was read at the meeting of the British Medical Association in Brighton, entitled "On an Apparently Peripheral Differential Action of Ether upon the

Laryngeal Muscles," by Felix Semon, M.D., F.R.C.P., and Victor Horsley, B.S., F.R.S. The authors were able to confirm the results of Hooper's experiments as to the effect of ether on the recurrent laryngeal nerve, and even gave a graphic representation of the "ether effect" studied by means of a rubber bulb inserted between the vocal cords. They explained Donaldson's failure to obtain the "ether effect" on the supposition that the animal was not sufficiently etherized. They also repeated Donaldson's experiments with currents of varying strength and obtained similar results in those cases in which the animal was not deeply under the influence of ether.

In view of these somewhat discordant results a renewed investigation of the effect of electrical irritation of the recurrent laryngeal nerve, with and without narcotics, seemed desirable, and Dr. Hooper is now engaged in a series of experiments which it is hoped will shed further light upon the subject.

The detailed results of these experiments will be published on some future occasion, but at the present time the following preliminary statement may be made.

It has not been found possible in these experiments to obtain a dilatation of the glottis by any stimulation of the recurrent laryngeal nerve unless the animal is under ether.

When the animal is etherized, the effect of irritating the nerve varies with the depth of the narcosis and the strength of the irritation.

If the animal is thoroughly under the influence of the drug dilatation of the glottis is produced by irritations of all intensities. In less profound etherization dilatation is still obtained with feeble irritation, but gives place to constriction when a stronger stimulus is applied.[1] As the effect of the ether passes off constriction occurs with feebler and feebler intensities until, finally, dilatation can no longer be obtained, and constriction is produced by irritation of all intensities.

The observation of Donaldson that dilatation is produced by feeble and constriction by strong stimuli is, therefore, correct *for a certain stage of etherization*, but for *unetherized* animals his statement has not been confirmed. The cases in which Donaldson has recorded a dilatation as a result of feeble stimulation are those in which the animal had been previously etherized, but was supposed to have recovered from the influence of the drug. In view of Hooper's failure to obtain dilatation on unetherized dogs, it seems probable that in Donaldson's cases the drug had not been completely eliminated.

It will thus be seen that, while the "ether effect," as shown on the sciatic nerve of the frog, may be explained as a partial paralysis of the nerve by the drug, the same explanation cannot be given of the phe-

[1] It will be observed that this result is in harmony with the above-mentioned observations of Semon and Horsley.

nomenon as manifested on the recurrent laryngeal nerve of the dog, for the action of ether cannot be imitated by feeble irritation of the nerves of unetherized animals.

The local action of ether, applied directly to the nerve, presents another point in which the two phenomena differ from each other, for the distinct "ether effects" obtained in this way by Perkins and Ellis on the frog's sciatic do not manifest themselves on the laryngeal nerve of the dog. A six per cent. solution of ether dropped upon the nerve of chloralized dogs, between the electrodes and the larynx, was found to gradually paralyze the nerve, so that stronger and stronger stimuli were needed to constrict the glottis, but a dilatation was, under these circumstances, never observed.

Conclusions.—The principal results of these various researches may be summarized as follows:

1. The ordinary effect of electrical stimulation of the recurrent laryngeal nerves of dogs is to cause constriction of the glottis, but if the animal is thoroughly etherized dilatation may be produced.

2. If the animal is partially etherized, the effect of the stimulation will vary with the strength of the current, a weak irritation causing dilatation, and a stronger irritation causing constriction of the glottis.

3. The more complete the etherization the greater is the intensity of the current necessary to produce constriction.

4. A similar "ether effect" may be observed when the sciatic nerve of the frog is stimulated, the ordinary extension of the leg and abduction of the toes giving place, under the influence of this drug, to flexion and adduction. It is, however, always possible to produce the ordinary effects by increasing the intensity of the stimulation; and, on the other hand, it is possible, by using very feeble stimuli, to produce without etherization the same effects which occur on the application of stronger stimuli to animals under the influence of the drug.

5. This "ether effect" on frogs may be observed both when the ether solution is introduced by cutaneous absorption, and when it is applied locally to the nerve below the point of stimulation. Hence the most reasonable explanation of the phenomenon is that the drug, by diminishing the conducting power of the nerve, causes a strong irritation applied to the nerve to become a weak irritation when it reaches the muscles.

6. This explanation cannot be applied to the phenomenon as exhibited by the recurrent laryngeal nerve of the dog, for without ether feeble irritations do not produce dilatation, and, with complete etherization, strong stimuli do not produce constriction of the glottis.

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